

REMARKS

The present application is directed to methods of cloning genes using replication-deficient baculovirus vectors. Prior to this Amendment and Response, Claims 27-34 were pending. In the present Amendment and Response, applicants amend Claims 27 and 30. The amendments do not introduce any new matter. Applicants amend Claim 30 to bring it into correspondence with the previously submitted Claim 29. Support for the amendment is indicated in the Response to Final Office Action filed July 19, 2004. Upon entry of the present amendment, Claims 27-34 will be pending.

Telephone Interview

Applicants thank the Examiner for extending the courtesy of a telephone interview on December 3, 2004.

Drawings

The Examiner maintains the objection to Figures 3B, 5 last panel, and 7 A-C under 37 CFR 1.83(a) asserting the drawings fail to show any details as described in the specification. The Examiner states that Figure 3 submitted on April 18, 2001, was clear and the bands in the depicted Northern Blot were visible. Accordingly, applicants respectfully request the Examiner to substitute the April 18, 2001 submission of Figure 3 for the copy of Figure 3 submitted with the previous Response.

Claim Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejects Claims 27-34 under 35 U.S.C. § 112, second paragraph, as indefinite.

Claim 27

The Examiner rejects Claim 27 under 35 U.S.C. § 112, second paragraph, as indefinite. The Examiner asserts that the term “encoding” recited in Claim 27 is unclear because “the vector does not “encode” other nucleic acid sequences or genes.” In the August 26, 2004 Non-Final Office Action and during the December 3, 2004 telephone interview, the Examiner recommended amending Claim 27 to recite “a rescue vector comprising.” Applicants herein amend Claim 27 to recite “a rescue vector comprising.” Applicants respectfully assert that the amendment overcomes the rejection of Claim 27 under 35 U.S.C. § 112, second paragraph, and request its withdrawal.

The Examiner asserts that the term “a nucleic acid sequence, which is capable of restoring replication” recited in Claim 27 is unclear because “[i]t is not clear how the nucleic acid sequence “is capable of restoring replication.” Applicants respectfully assert that the nucleic acid sequence can, for example, encode a protein capable of restoring replication or comprise a control sequence that is necessary for expression of a gene capable of replication (see page 6, last paragraph, of the specification). Accordingly, applicants respectfully assert that the term “a nucleic

acid sequence, which is capable of restoring replication” is clear to one of the ordinary skill in the art. In view of the foregoing amendments and arguments, applicants respectfully request that the rejection of Claim 27 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claims 29-30

The Examiner rejects Claim 29-30 under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse the rejection.

The Examiner asserts that the term “a functional gene” recited in Claims 29-30 is unclear. The Examiner states that “[i]t is unclear what criteria are required to distinguish a “functional gene”.” Applicants respectfully disagree. The specification defines the term “a functional gene” on page 6, second and third full paragraph. One of ordinary skill in the art in the field of virology would understand the term “a functional gene” to mean a gene capable of performing its normal function, specifically, a gene required for viral replication.

In support of their position, applicants submit herewith for the Examiner’s consideration a Declaration under 37 C.F.R. §1.132 (hereinafter referred to as “the Declaration”) by Dr. Robert David Possee, an expert in the field of the invention and a named inventor of the present patent application. Applicants respectfully bring to the Examiner’s attention Section 3 of the Declaration, where Dr. Possee asserts that one of ordinary skill in the art would know the meaning of the term “a functional

gene.” In view of the foregoing, applicants respectfully request withdrawal of the rejection of Claims 29-30 under 35 U.S.C. § 112, second paragraph, as indefinite.

The Examiner maintains that Claims 29-30 are vague and indefinite because the term “a functional gene necessary for restoring a functional gene” is unclear. The Examiner states that “[i]t is unclear if this gene is a functional gene required for viral replication or a gene that enzymatically restores the functional gene to its replication competent status.” Applicants respectfully disagree. Applicants respectfully assert that the term “a functional gene necessary for restoring a functional gene” recited in Claim 29 would be understood by one of ordinary skill in the art in the field of virology to mean a gene whose product replaces a non-functioning gene product. The specification defines the meaning of the term “a functional gene necessary for restoring a functional gene” on page 6, third full paragraph.

In support of their position, Applicants respectfully bring to the Examiner’s attention Section 4 of the Declaration, where Dr. Possee asserts that one of ordinary skill in the art would know the meaning of the term “a functional gene necessary for restoring a functional gene.” In view of the foregoing, applicants respectfully request withdrawal of this rejection of Claims 29-30 under 35 U.S.C. § 112, second paragraph.

Claims 31 and 32-34

The Examiner rejects Claims 31 and 32-34 under 35 U.S.C. § 112, second paragraph, as indefinite, asserting that the term “functional gene” is unclear. Applicants respectfully traverse the rejection. As note in the previous section, applicants respectfully assert that the term “a functional gene” means a gene required for viral replication. Applicants respectfully request withdrawal of this rejection of Claims 29-30 under 35 U.S.C. § 112, second paragraph.

Claims 31-34

The Examiner rejects Claims 31-34 under 35 U.S.C. § 112, second paragraph, as indefinite, asserting that the term “functional fragment or mutation thereof” is unclear. Applicants respectfully traverse the rejection.

The Examiner states that it is unclear how the functional gene can be a fragment or a mutation. Applicants respectfully bring to the Examiner’s attention that different mutations can produce genes can be deleted that are still functional and retain at least a part of their activity. Parts of genes can be deleted to produce fragments that retain the activity of that gene. Applicants demonstrated in the present application that deleting part of a gene *ORF 1629* results in its functional fragment (see p. 28 of the specification). The term “functional fragment and mutation thereof” recited in Claim 31-34 would be understood by one of ordinary skill in the art in the field of virology to mean genes comprising mutations and/or deletions, yet retaining

at least a part of their activity. In support of their position, applicants respectfully bring to the Examiner's attention Section 5 of the Declaration. Applicants respectfully request withdrawal of this rejection of Claims 31-34 under 35 U.S.C. § 112, second paragraph.

Claim Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejects Claims 27-34 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

New matter rejection of Claim 27 due to the term "naked"

The Examiner rejects Claim 27 due to the term "naked" added in the previous amendment. The Examiner asserts that she does not find support in the originally filed specification for the term "naked." Applicants respectfully traverse the rejection.

Applicants respectfully assert that the specification provides implicit support for the term "naked" recited in Claim 27. Furthermore, applicants respectfully bring to the Examiner's attention Section 6 of Dr. Possee's declaration to support their position that one of ordinary skill in the art would know that the term "naked," recited

in Claim 27 in reference to a baculovirus vector, is implicitly supported by the specification.

Based on the specification, one of ordinary skill in the art would understand “naked” to mean that the baculovirus vector is without binding proteins (in the case of virus DNA, without the protective particles). The term “naked” is used by those of ordinary skill in the art in reference to nucleic acids that are at least partially devoid of the proteins that usually accompany those nucleic acids (see Exhibits C and D associated with the Declaration). The claimed baculovirus vector is used without a viral particle. It is naked, or without at least a part of its coat of viral protein.

The specification provides at least the following support for a baculovirus vector DNA that is naked, or without at least a part of its coat of viral proteins. On page 6, third paragraph, the specification discloses that the baculovirus nucleic acid is DNA. On page 15, second paragraph, the specification shows that the DNA is prepared by extracting it from yeast, not from a viral particle. The DNA is purified on a sucrose gradient and is ethanol precipitated. These methods produce naked DNA because the viral particle cannot be made in yeast. Furthermore, it is clear from the specification that the DNA is naked, because transfection of the naked DNA into cells requires lipofectin (see p. 17, bottom). If the DNA was not naked, lipofectin would not have been necessary. The co-transfection described on page 33, final paragraph, also uses the naked baculovirus vector. Thus, based on the specification, one of ordinary skill in the art would know that naked baculovirus vector is used, and that

the term “naked” is implicitly supported by the specification. In view of the foregoing, applicants respectfully request that the rejection of Claim 27 under 35 U.S.C. §112, first paragraph, due to the term “naked” be withdrawn.

Claims 31-34

The Examiner maintains the rejection of Claims 31-34 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse the rejection.

The Examiner asserts that the applicants have not provided a disclosure sufficient to show that applicants were in possession of a claimed genus of the functional genes *lef 1-12*, *dnapol*, *pl43*, *p35*, *ie-1-2*, *p47*, *ORF 1629* and *pp 31* and functional fragments and mutations thereof. Applicants respectfully disagree. It is the applicants position, explained in the previously filed Response, that the application, as filed, conveys to one of ordinary skill in the art that the functional genes, a representative number of which is disclosed in the specification, and their functional fragments and mutations, fall within the claimed method of cloning a gene using a replication-deficient baculovirus vector.

At the priority date of the present application, the genes recited in Claims 31-32 were all known to be involved in baculovirus replication, as stated in the

specification on page 6, second full paragraph. The application provides the references and clear instructions that could be readily used by a person of ordinary skill in the art in routine experiments to create the claimed vectors. Thus, based on the teachings provided in the specification and the available knowledge, one of ordinary skill in the art would know how to use the genes recited in Claims 31-32. In support of their position, applicants respectfully refer the Examiner to Section 7 of the Declaration, where Dr. Possee, an expert in the field of virology, states that one of ordinary skill in the art would know that the specification describes the functional genes recited in Claims 31-32 in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner asserts that “functional fragments or mutations thereof” recited in Claims 31-32 must be empirically determined, and that applicants have not reduced to practice the claimed invention. Applicants respectfully disagree. The genes recited in Claims 31-32 were known at the priority date of the present application. It was also known at the priority date that variations of genes in general occur naturally or can be introduced artificially through routine experimentation, and that different mutations can produce genes that are still functional and retain at least a part of their activity.

Experiments to identify mutants and create functional fragments are routine for a person of ordinary skill in the art. At the time of filing of the present

application, the complete genomes of five baculoviruses had been completely sequenced. Different baculovirus genes similar to the genes recited in Claims 31-32, but smaller in size or with a slightly different nucleotide sequence, were known. In spite of these differences, the similar genes from different baculoviruses retained their function. One of ordinary skill in the art would know how to identify functional fragments and mutations at least based on the routine comparison of the nucleotide sequence of the recited genes to similar genes from different baculoviruses. Thus, one of ordinary skill in the art would be able to apply the teachings of the present application to the genes recited in Claims 31-32 to identify their functional fragments and mutations.

In support of their position, applicants respectfully bring to the Examiner's attention Section 8 of the Declaration, where Dr. Possee states that experiments to identify mutants and create functional fragments of the recited genes are well within the capabilities of a person of ordinary skill in the art. In view of the foregoing, applicants respectfully request withdrawal of the rejection of Claims 31-34 for reasons of insufficient written description under 35 U.S.C. §112, first paragraph.

Claim Rejections under 35 U.S.C. §103(a)

Clark in view of Patel

The Examiner maintains the rejection of Claims 27-34 under 35 U.S.C. §103(a) as obvious over Clark *et al.* (hereinafter *Clark*), in view of Patel *et al.* (hereinafter *Patel*). Applicants respectfully traverse the rejection.

The Examiner asserts that one of ordinary skill in the art at the time of the invention would have been motivated to combine the teachings of *Clark* with the teachings of *Patel*, and that the combination would result with a reasonable expectation of success in the applicants' invention, as claimed. Applicants respectfully disagree.

Applicants disclose and claim a novel method of cloning genes using replication-deficient baculovirus vectors. This method possesses a number of unexpected advantages over known methods. These advantages are described in Section 9 of Dr. Posse's Declaration. The claimed method allows for production of a pure population of recombinant baculovirus not contaminated with the parental baculovirus, considerably reducing time and money required to produce recombinant proteins. The method uses an intermediate host, such as bacteria or yeast, for production of large quantities of the replication-deficient parental baculovirus DNA that cannot replicate in insect cells. The intermediate host allows for easy maintenance of the parental baculovirus and for amplification of large amounts of the

virus DNA. The method uses naked purified baculovirus DNA that can be stably stored without storage affecting its infectivity. Using naked DNA allows for co-transfection of the baculovirus vector and foreign DNA, which saves time and money. As compared to the previously described two-step methods that involve separate transfections of the viral and the foreign DNA, co-transfection eliminates the requirement for accurate timing of the two separate transfections that is necessary for obtaining recombinant baculoviruses.

Clark *et al.* (hereinafter *Clark*) fails to teach, suggest, or provide motivation to derive applicants' claimed invention and fails to render it obvious. *Clark* suggests a recombinant baculovirus expression system that that uses replication enablement as a selectable marker. As previously submitted by applicants in the response filed July 19, 2004, modifying the replication-deficient baculovirus expression system in *Clark* with a yeast or bacterial origin of replication will not result in the advantages of the claimed method. Applicants previously described the disadvantages of the system suggested in *Clark* (see the July 19, 2004 Response), which are also outlined in Section 10 of Dr. Possee's declaration (publications cited herein are enclosed as Exhibits E-G).

Clark suggests using the p35 gene as a selectable marker. The parental p35-deficient baculovirus would have to be amplified in apoptosis-deficient cell line, which will result in the parental baculovirus' mutations and will be detrimental to the expression of the very late genes. Even if the recombinant baculovirus vectors in

Clark were modified with a yeast or bacterial origin of replication, upon recombination in insect cells, the *Clark* baculovirus would be contaminated by parental stock, because the defective parental virus in *Clark* can still replicate at a low levels in the Sf9 cells that *Clark* uses for recombination. Thus, in contrast to the applicants' claimed method, the method suggested in *Clark* will fail to produce the recombinant viruses free of the parental stock even if the parental viruses were modified with a yeast or bacterial origin of replication as suggested by the Examiner.

It is applicants' position that one of ordinary skill in the art would not be motivated to modify the teachings of *Clark* to derive the applicants' invention as claimed. The Examiner asserts that it is within the ordinary skill in the art to "express replication defective baculovirus in a cell," but *Clark* fails to teach or suggest replicating its defective baculovirus in an intermediate host cell, in contrast to applicants. *Clark* discusses known methods of using yeast and bacterial cells to accomplish baculovirus recombination (see column 2, bottom two paragraphs), but fails to teach or suggest using bacteria or yeast for amplification of the parental baculovirus. With the benefit of hindsight one might consider changing the cells, but *Clark* fails to suggest or provide motivation for such a change.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to modify the virus in *Clark* with the yeast or bacterial origins of replication of Patel *et al.* (hereinafter *Patel*), which teaches a method that involves recombination in yeast cells, however *Clark* teaches away from using such methods by referring to

them as “cumbersome and complicated” (see column 2, line 44). Thus, based on the teachings of *Clark*, one of ordinary skill in the art would not be motivated to modify the method in *Clark* based on the teachings of *Patel*. In support of their position, applicants respectfully bring to the Examiner’s attention Section 10 of Dr. Possee’s Declaration.

In itself, *Patel* fails to teach, suggest, or provide motivation to derive applicants’ claimed invention and fails to render it obvious. One of ordinary skill in the art in the field of virology would not be motivated by the teachings in *Patel* to derive the claimed invention. In contrast to the applicants’ claimed method, *Patel* uses the yeast cells for recombination (that is, to modify the baculovirus), but not for maintenance of the baculovirus. As noted in Dr. Possee’s Declaration (Section 11), *Patel* fails to attain the economy of time that is achieved in the applicants’ claimed method that is simpler, more efficient, and easier to use than the method in *Patel*.

In contrast to *Patel*, in applicants’ claimed method the intermediate host is used for maintenance of the defective baculovirus, and the insect cells are used for recombination. Applicants previously brought the to the Examiner’s attention (see July 19, 2004 Response) that *Patel* fails to teach an intermediate host for the parent defective baculovirus and teaches away from using insect cells for recombination. *Patel* teaches using insect cells for plaque purification (see page 99, last paragraph), but the lowering of parental virus background in *Patel* is achieved by using yeast cells and avoiding insect cells at the recombination stage. As supported by Section 11 of

Dr. Possee's Declaration, based on the teachings of *Patel*, one of ordinary skill in the art would not be motivated to use the insect cells for recombination, and would not be motivated to combine the teachings of *Patel* with the teachings of *Clark*. Thus, *Clark* and *Patel*, separately or in combination, fail to teach, suggest, or provide motivation to derive the claimed invention. As supported by Dr. Possee's Declaration, based on the teachings of *Clark* and *Patel*, one of ordinary skill in the art would be directed away from modifying either method to derive applicants' invention, as claimed.

In view of the foregoing, applicants respectfully assert that that one of ordinary skill in the art would not be motivated to combine the teachings of *Clark* and *Patel* to derive the applicants' invention, as claimed. Furthermore, modification of the teachings of *Clark*, as suggested by the Examiner, would fail to result in a method possessing the advantages of applicants' invention. Applicants respectfully assert that *Clark* and *Patel*, separately or in combination, fail to render applicants' invention obvious. Applicants request withdrawal of the rejection under 35 U.S.C. §103(a) over *Clark* in view of *Patel*.

Kitts in view of Patel

The Examiner maintains the rejection of Claims 27-34 under 35 U.S.C. §103(a) as obvious over *Kitts et al.* (hereinafter *Kitts*) in view of *Patel*. Applicants respectfully traverse the rejection.

The Examiner asserts that one of ordinary skill in the art at the time of the invention would have been motivated to combine the teachings of *Kitts* with the teachings of *Patel* to achieve economy of time and reduce costs, and that the modification would result in applicants' invention, as claimed, with a reasonable expectation of success. Applicants respectfully disagree.

As applicants stated previously (see July 19, 2004 Response), *Kitts* fails to teach, suggest or provide motivation to derive applicants' invention, as claimed, and fails to render it obvious. It is applicants' position, supported by Dr. Possee's Declaration (see Section 12), that one of ordinary skill in the art would not be motivated to derive the claimed invention by combining the teachings of *Kitts* and *Patel* as suggested in the Office Action mailed August 26, 2004.

Kitts teaches a method of producing a recombinant baculovirus vector in insect cells that uses baculovirus DNA linearized with a restriction enzyme in combination with standard transfer vectors. *Kitts* fails to teach the use of an intermediate host. Applicants respectfully assert that *Kitts* fails to teach, suggest or provide motivation to modify its method to derive the applicants' invention as claimed. But even if one were to modify the method in *Kitts*, as suggested by the Examiner, the resulting method would lack the advantages of applicants' claimed method. As previously noted by applicants and supported by Section 11 of Dr. Possee's Declaration, using linearized baculovirus DNA results in parental virus DNA contamination when attempting to make a recombinant baculovirus. Thus, a method using linearized

parental virus DNA, such as the one taught in *Kitts*, lacks the advantages of the applicants' claimed method.

Applicants respectfully assert that *Patel* fails to teach, suggest, or provide motivation to derive applicants' invention as claimed and fails to provide motivation to modify its teachings as suggested by the Examiner for the reasons provided in the previous section. As noted above, *Patel* fails to teach the use of insect cells for recombination and provides motivation to avoid using insect cells for this purpose. Thus, one of ordinary skill in the art would not be motivated to combine the teachings of *Kitts* and *Patel*, as supported by Section 11 of Dr. Possee's Declaration.

In view of the foregoing, applicants respectfully assert that one of ordinary skill in the art would not be motivated to combine the teachings of *Kitts* and *Patel* to derive applicants' invention, as claimed, with a reasonable expectation of success. Furthermore, modification of the teachings of *Kitts*, as suggested by the Examiner, would fail to derive applicants' invention, as claimed, and would fail to result in a method possessing the advantages of applicants' invention. Applicants respectfully assert that *Kitts*, separately or in combination with *Patel*, fails to render the applicants' invention obvious. Applicants request withdrawal of the rejection under 35 U.S.C. §103(a) over *Kitts* in view of *Patel*.

CONCLUSION

Applicants respectfully submit that this is a complete response to the Non-Final Office Action dated August 26, 2004. Applicants respectfully assert that the claims are now in condition for allowance and request that the application be passed to issuance. If the Examiner believes that any informalities that may be corrected by Examiner's amendment remain in the case, or if there are any other issues which can be resolved by a telephone interview, a telephone call to the undersigned agent at (404) 815-6102 is respectfully solicited.

Respectfully submitted,



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